Original Abstract

Proteasome inhibitors (PIs) are currently a mainstay treatment for multiple myeloma (MM). Unfortunately, cure is rare. Here, we attempted to define mechanisms for acquired PI resistance in MM cell lines. Two PI-resistant MM cell lines were serendipitously developed by blasticidin exposure. These cells had Unfolded Protein Response (UPR) profiles resembling their PI-sensitive isogenic parental cell lines. PI resistance was demonstrated to be due to Mycoplasma infection, which was found to interfere with drug inhibition of the proteasome target. Screening of patient samples did not reveal mycoplasma infection of primary MM cells, suggesting that this may be primarily an *in vitro* phenomenon. Instead, gene expression analyses of primary MM samples suggested that epigenetic dysregulation (revealed by ectopic cancer testis antigen expression) correlates with clinical bortezomib resistance. We therefore screened a panel of small molecule epigenetic probes to identify regulators of PI response. Most epigenetic probes had no effect on PI response. However, MM cell inhibition and bortezomib sensitization was observed with the pan-BET inhibition, JQ1, suggesting that additional pre-clinical and clinical evaluation of PIs in combination with BET (or BRD4) inhibitors is warranted.